Chapter 10
Pediatric Liver Disease

A1a. Characterize clinical syndrome, natural history, etiology, cofactors, and complications of pediatric NASH. The histologic features of NASH are different in children than in adults (Schwimmer JH. *Hepatology* 2005;42:641). A scoring system for NAFLD for use in clinical investigation, natural history studies and therapeutic trials has been developed by the NIH-funded NASH Clinical Research Network (Kleiner DE. *Hepatology* 2005;41:1313). (10%)

A1b. Develop definitions and diagnostic criteria for the major neonatal cholestatic syndromes. Investigators in the NIH-funded Biliary Atresia Research Consortium (BARC) and Cholestatic Liver Disease Consortium (CLiC) have developed clinical definitions and diagnostic criteria for the major neonatal cholestatic syndromes for use in an observational longitudinal study. (10%)

A2. Develop systems to better characterize the frequency, medical burden, and epidemiology of pediatric liver disease. Epidemiologic research is a component of several NIH-supported studies, including the NASH Clinical Research Network, BARC, CLiC, the Pediatric Acute Liver Failure Study Group (P-ALFSG), the Peginterferon and Ribavirin for Pediatric Patients with Chronic Hepatitis C (Peds-C) trial and the SPLIT pediatric liver transplant registry. (0%)

A3. Elucidate the major cause of idiopathic acute liver failure in children. The ongoing ALFSG has shown that 52% of cases of acute liver failure in children are of unknown etiology. Investigation of abnormal bile acid metabolism, viruses, toxins, cytokines, abnormal immunological responses and inborn errors of metabolism such as fatty acid oxidation defects are a part of ancillary studies of the recently funded Pediatric ALFSG. (0%)

B1a. Define structural and functional development of the liver and biliary system. The transcription factors Foxa and GATA6 play critical roles in the embryogenesis of the liver (Lee CS. *Nature* 2005;435:944; Zhao R. *Mol Cell Biol* 2005;25:2622). Using novel approaches to label embryonic cells, the anatomical disposition of cells during patterning of the embryonic endoderm has been described (Temblay KD. *Dev Biol* 2005;280:87). Studies in zebrafish have shown the critical role of networks of transcription factors and signaling pathways in development of the biliary tree (Sadler KC. *Development* 2005;132:3561). (20%)

B1b. Evaluate long-term outcomes, complications, and tolerance-inducing regimens in children undergoing liver transplantation. Analysis of data on children who receive liver transplants from the United Network for Organ Sharing (UNOS) has shown that smaller reduced liver grafts, life support at transplantation, and younger age are associated with increased post-transplant mortality (Barsches NR. *Liver Transpl* 2005;11:1193). The NIH-funded SPLIT registry has identified nutrition as an important and potentially modifiable risk factor for post-transplant outcomes (Utterson EC. *J Pediatr* 2005;147:180). (10%)

B2a. Delineate the molecular pathogenesis of at least 3 of the neonatal cholestatic syndromes. A specific focus of the NIH-funded CLiC consortium is to define the molecular pathogenesis of all of the neonatal cholestatic syndromes. (0%)

B2b. Develop better animal models for neonatal cholestatic syndromes. Genetic and immunologic studies in a mouse model of rotavirus-induced neonatal biliary injury shows that it recapitulates key liver and biliary features found in children with biliary atresia (Carvalho E. *Gastroenterology* 2005;129:713; Mack CL. *Clin Immunol* 2005;115:200). Two mouse models have been further characterized with inactivation of the following genes associated with neonatal cholestatic syndromes: Abc11 (Henkel A. *Mamm Genome* 2005;16:903) and Abcb4/Mdr2 (Popov Y. *J Hepatol* 2005;43:1045). The NIH encourages research in this area through PA-05-049: "Animal Models of NIDDK-Relevant Diseases." (20%)

B3. Identify biomarkers for diagnosis, staging, and grading of neonatal cholestatic syndromes. NIH-funded investigators participating in CLiC are developing study protocols to diagnose, stage, and grade cholestatic syndromes and will be testing a novel customized re-sequencing gene chip and proteomics technology for use in identifying biomarkers of pediatric cholestasis. (0%)

C1a. Conduct clinical trials to optimize medical and surgical management of biliary atresia. NIH-funded BARC investigators have initiated a prospective randomized, placebo-controlled trial of corticosteroids after portoenterostomy in infants with biliary atresia. (10%)

C1b. Evaluate therapies for acute liver failure in children. Investigators in the newly created NIH-funded Pediatric ALFSG have initiated a prospective, randomized controlled trial of N-acetyl-cysteine as a medical treatment for children with acute liver failure. (10%)

C2. Based upon molecular pathogenesis, identify small molecule therapies that might alleviate neonatal cholestatic syndromes. Targets for small molecule therapies include the nuclear hormone receptors that regulate bile acid and anion transport and secretion. *In vitro*, high-throughput screening of small molecules with possible use in neonatal cholestatic syndromes is encouraged through the Roadmap trans-NIH RFA "Assay Development for High Throughput Molecular Screening" (RM-05-011). (0%)

C3a. Define the etiology of biliary atresia. This goal is the major focus of the BARC Consortium, which is enrolling patients and collecting clinical data, serum DNA, and liver and biliary tissue for investigation of the etiology of this disease. Ancillary studies to use the resources generated by the BARC Consortium are encouraged in a program announcement on "Ancillary Studies to Major Ongoing NIDDK Clinical Research Studies" (PAR-04-082); several of these studies have been funded. (0%)

C3b. Develop gene, siRNA, cell transfer, or stem cell therapy for pediatric metabolic disease. Both NIH- and industry-funded research investigators are extremely active in this area. (0%)

Figure 12. Estimated Progress on Pediatric Liver Disease Research Goals, 2005 (Year 1)